Genomic Profiles of Early-Stage Non-Small Cell Lung Cancer Patients, and Association with Pre-Treatment Blood Circulating Tumor DNA Detection and Levels

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Introduction

How do tumor genomic profiles relate to ctDNA detection?

Early-stage non-small cell lung cancer (NSCLC) is treated with curative intent, but a significant proportion of patients experience recurrence

Circulating tumor DNA (ctDNA) offers a minimally invasive means of detecting molecular residual disease and provides prognostic information before and after treatment[1,2]

ctDNA detection rates vary widely among patients, even within the same stage

The influence of tumor characteristics, including driver gene mutation status, on ctDNA detection and quantity, remain little explored

Here we explore associations between tumor genomic profiles and pre-treatment ctDNA detection and levels in NSCLC

Methods

165 patients with stage 0-III NSCLC were recruited to two retrospective clinical studies; LUCID[1] (n=78) and LEMA[2] (n=87)

Whole exome sequencing (WES)-identified somatic tumor mutations were compared to plasma pre-treatment (pre-Tx) ctDNA detection using personalized panels (RaDaR 1.0)

Pre-Tx samples were prioritized to limit confounding effects of treatment

Analyses focused on the association of mutation status* of select tumor driver genes (TP53, KRAS, EGFR) with pre-Tx ctDNA detection and estimated Variant Allele Fraction (eVAF), and survival

Biological and clinical characteristics such as tumor stage, smoking status, and histology (**Table 1**) were also explored

*Variants matched a hotspot whitelist: EGFR known sensitizing mutations and exon-19 deletions, KRAS codon 12/13/61 variants, and TP53 canonical hotspots and truncating events

Characteristic		Number (%)
n patients		165
Sex	F	75 (45.5)
	M	90 (54.5)
Stage	0/I	88 (53.3)
	II	36 (21.8)
	III	41 (24.8)
Subtype	LUAD	102 (61.8)
	Non-LUAD	63 (38.2)
Smoking status	Current or Ex	153 (92.7)
	Never	12 (7.3)

Cohort Characteristics

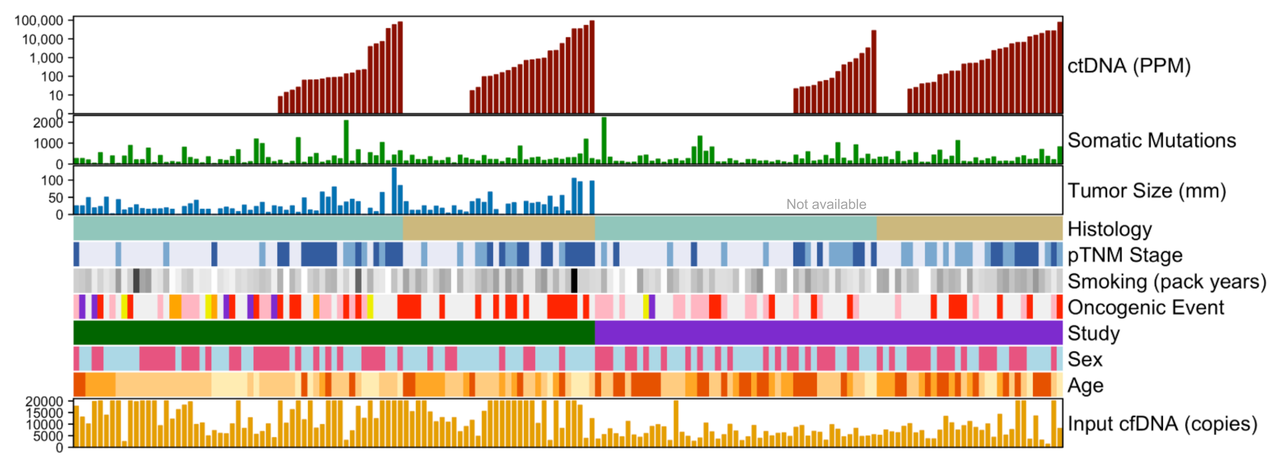

Figure 1: *Heatmap showing patients (n =165) with clinical and pathological covariates annotated. Key 'Oncogenic Events' in TP53, KRAS and EGFR per tumor-WES as well total number of somatic mutations are included*

Tumor Genomic Profiling

The median number of WES-identified somatic tumor variants across the cohort was 237

Oncogenic event rates (per hotspot whitelist) were 22.4%, 20%, 3.6%, and 4.8% for TP53, KRAS, EGFR, and multi-hits (TP53-KRAS or TP53-EGFR) respectively **(Figure 2A)**, though the mutation distribution differed by histological subtype (p=1.8e-05; **Figure 2B)**

There was a significant difference in total mutation burden among genomic groups (Kruskal p = 0.027) with a trend towards higher burden in TP53 and KRAS mutant groups **(Figure 2C)**

Similarly, smoking history (pack years) was positively correlated with somatic mutation burden (p < 0.001)

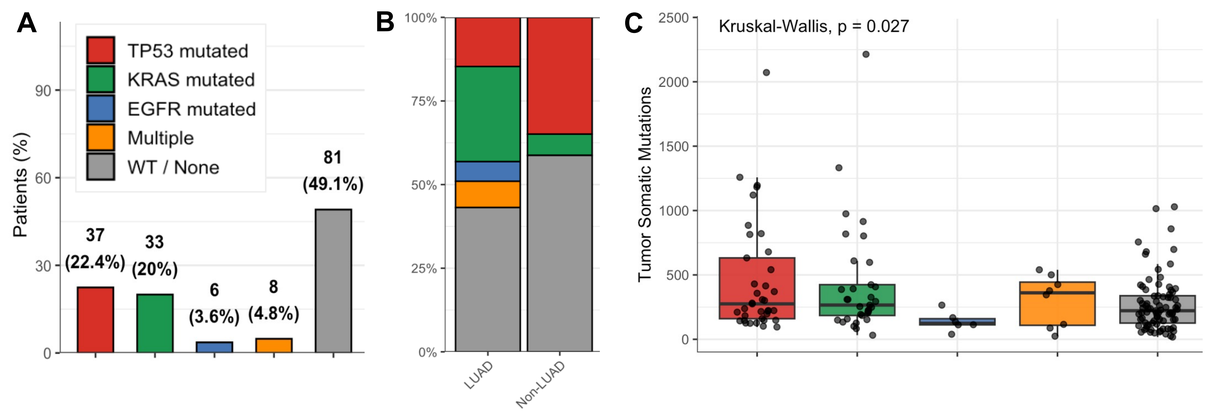

Figure 2: ***(A)*** *Frequency of major oncogenic driver whitelist events identified by WES.* ***(B)*** *Distribution of oncogenic events by histological subtype (LUAD; lung adenocarcinoma, Non-LUAD)* ***(C)*** *Comparison of total tumor mutation burden across genomic subgroups*

Tumor Profile – Association with ctDNA Detection

Patients with ctDNA detected pre-Tx had tumors with a higher mutation burden (p<0.05) (**Figure 4A**)

ctDNA detection differed by mutation group (p<0.001**)** (**Figure 4B**) but ctDNA levels (ppm) did not (p=0.88) (**Figure 4C**)

After adjusting for covariables, TP53 mutant tumors had higher rates of ctDNA detection (p<0.05) (**Figure 4D**)

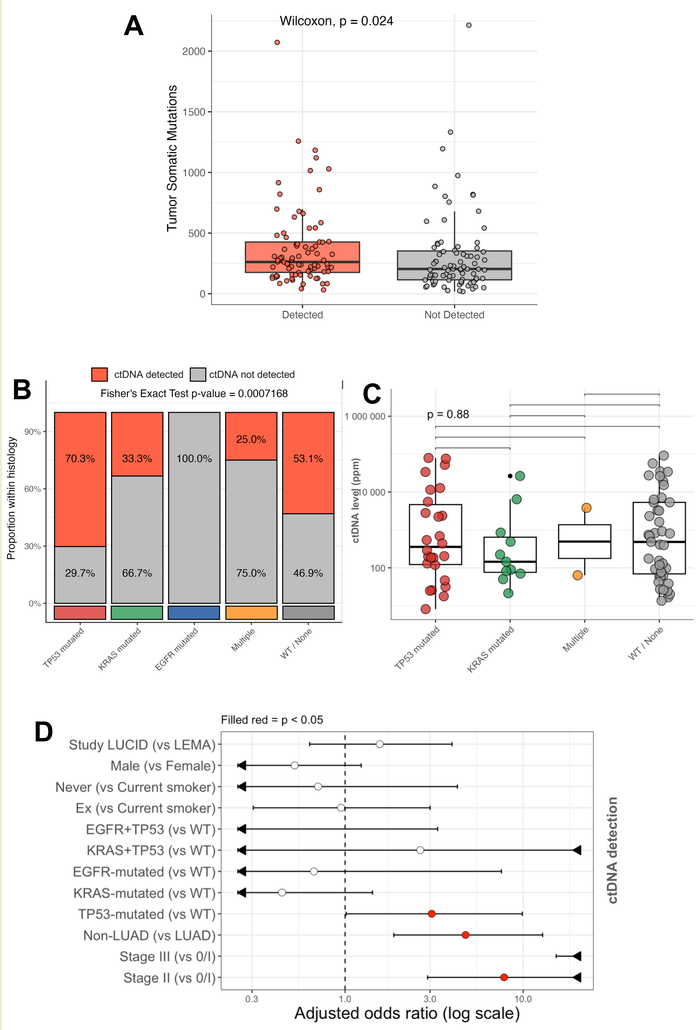

Figure 3: ***(A)*** *Tumors with pre-Tx ctDNA detected had more somatic mutations (p=0.024).* ***(B)*** *ctDNA detection differed by mutation group (p<0.001), but* ***(C)*** *ctDNA levels did not (p=0.88).* ***(D)*** *In multivariable analysis, TP53 mutation and higher stage independently predicted ctDNA detection (p<0.05)*

Tumor Profile – Association with Survival

ctDNA detection pre-Tx was associated with worse overall-(OS) and relapse free-(RFS) survival

Highlighting the importance of assay sensitivity, ctDNA detection at low levels (<100 ppm) trended towards being prognostic, though was not significant upon multivariable analysis

Despite its association with ctDNA detection, tumor TP53 mutations were not associated with OS or RFS, and there was no TP53 – ctDNA detection interaction

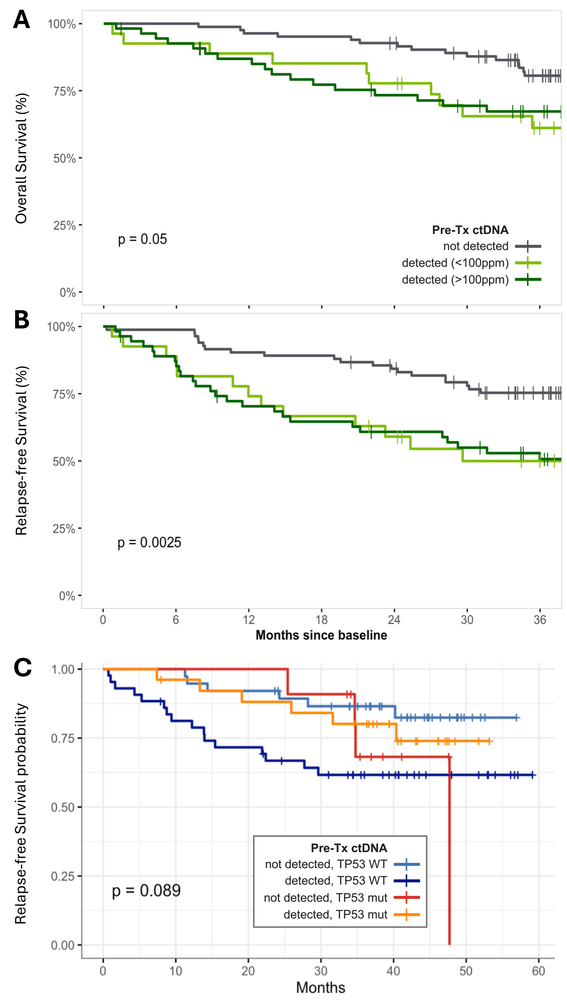

Figure 4: ***(A–B)*** *Pre-Tx ctDNA detection was associated with worse OS (p=0.05) and RFS (p=0.0025).* ***(C)*** *TP53 mutation status was not prognostic, and no ctDNA–TP53 interaction was observed*

Conclusions

Tumor genomic profiling revealed mutations in key cancer genes, with levels differing by disease subtype

ctDNA was more frequently detected pre-Tx in patients with TP53 mutant tumors. This echoes observations in breast cancer[3], and suggests a biological link between this gene, and the mechanism(s) of ctDNA shedding

Despite this association, TP53 mutation status was not linked to survival, though patient numbers were small

These data warrant further exploration of the link between the genomic make up of a patient's tumor, and the detection rate and levels of ctDNA

Further analysis is on-going, including expansion to a larger NSCLC cohort for greater statistical power, and exploration of pan-cancer associations

References:

1, Gale et al. Ann Oncol. 2022 May;33(5):500-510
2, Schuurbiers et al. PLoS Med. 2025 Apr 15;22(4):e1004574
3, Lipsyc-Sharf et al. ESMO Open, Volume 10, 104591

Conflict of Interest:

Authors with affiliation 1 are employees of NeoGenomics Laboratories Inc.

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